DR. McKUSICK: Thank you very much, Francis. That was tremendous.

Our next speaker is the Director of the National Institutes of Health, Harold Varmus. He has been director at the NIH since 1993. Prior to that, from about 1971 to 1993, he worked at UCSF. He received the Nobel Prize, shared the Nobel Prize in 1989. He is going to speak to us about science policy in the next forty years I guess, will talk about science policy at any rate.

DR. VARMUS: Thank you, Victor. The one thing I definitely contribute to this symposium is a good pointer.

[Laughter.]

DR. VARMUS: I want to be remembered for that if nothing else.

Victor, thank you very much. It is a great pleasure for me to be here. I enjoy very much my opportunities to come to the Jackson Lab and recreate and to talk science, and this is no exception.

I won't have an occasion at dinner tonight to say anything about you, Victor, but I do want to make one point that hasn't been made yet, a point that I think is very important. And that is in your many contributions to science, you have illustrated one aspect of the scientific personality that is often neglected, and that is altruism. And that the way in which you have put together your knowledge and made it available in the public forum has been a model for how genomic sequence is distributed by the NIH and our collaborators in the Genome Project. It is the model that I use myself in advocating for distribution of scientific publications through e-biomed. And I hope that that model will prevail in most of what we do despite the contentious and commercial times in which we live.

Now I have one obvious disadvantage in this meeting being the last official speaker. I have one advantage however in not being asked to talk about genetics. And, indeed, it has been

like going to a concert and hearing many performers play lovely music on lots of different themes. But my theme is going to be entirely different. However, while I am pledged to talk about policy, I am not going to talk about policy in the conventional sense, nor will what I say be entirely divorced from genetics because, indeed, as you have already heard, especially in the panel discussion, it really is impossible to disassociate genomics or genetics and policy.

First of all, genetics costs money and policy is often about money. Genetics and genomics cost post-doc lives, and that too is influenced by policies we have about training and financing of science. The changes you have heard about in biomedical science, we all do, indeed, profound changes that affect our technology and our goals and the application of our research to human health is going to require changes in funding mechanisms that we use, changes in the training procedures that we employ. These are clearly topics in the realm of policy that I could have talked about, but, indeed, am not going to talk about.

And there are other aspects of policy, some touched upon by LeRoy Walters, issues related to genetic privacy, and to discrimination, Francis mentioned, which again could be subjects for discussion. But it seems to me it is very hard to know where exactly we are going to be on many of those issues, whether it is stem cell research or others, forty years from now. And I have decided instead to talk about something which may on the surface sound rather bureaucratic, and that is the organization of the NIH.

Now in a moment I will tell you why I have chosen this topic, what the motivation was, but I have to lay out a few baseline assumptions here. First, I am making the assumption that over the next forty or fifty years that in general we will have a similar funding environment for research that we have now; namely, a pluralistic mechanism for funding research in which there is money coming from the pharmaceutical industry and the biotech industry, on the one hand, in

which there is money coming from states and from voluntary organizations, like the Heart Association, Cancer Association, and money coming from the Federal Government from multiple agencies, not just the NIH, but the NSF, the DOE, perhaps in somewhat changed form, as we are currently seeing, from the Department of Defense, and others.

I believe there will continue to be strong federal support for science, otherwise my predictions would have very little force. And I believe that because I think we have all been quite successful in the endeavor as promoted by the NIH to advance public health through science. On the other hand, we have to recognize that there are dangers to the federal funding of research and those dangers come from various sources, some of which are rather subtle, not simply the Balanced Budget Act of 1997, but also from more subtle forces like the Government Performance and Results Act which is now asking all government agencies to take account of their productivity. The advances that medicine has made in making the population older has a downside and the social cost to the Federal Government of maintaining the health of older individuals is going to place a heavy fiscal responsibility on government which in an era of concern about tax reduction could have negative effects on our ability to support the science that could actually make old age a better thing.

Now the first overhead shows you how I got into this topic of the organization of the NIH. About four weeks ago when I first started thinking what am I going to say after all these distinguished geneticists have talked, I ran across an article in the New York Times that I think occurred on a Saturday when they have an ideas and philosophy sort of page near the end of the first section, and this picture comes from a little essay about a delegate from Massachusetts to the Constitutional Convention of 1787, a man named Elbridge Gerry, referred to as bombastic idiot by most of his colleagues, but who nevertheless had a very influential effect on the formation of

our country because, perhaps against his better instincts, he decided to vote along with his Massachusetts delegate colleague for a Constitution in which the Senate allows two members from each state to have a vote.

That obviously allowed the Federal Government to work better as a Federal Government, it allowed states to have a more equal sense of representation. And the argument made in a book, one of these "What If" books, is that if Gerry had not voted the way he had that our country would not be as capable as a federal institution to, say, wage war against England in 1812, and instead would have evolved into a series of nation states, that are shown here. These are obviously highly speculative, but the idea would be that instead of having one nation with increasing numbers of states, that instead we would have these nation states, some of which would be doing much better than others, and some would be successes, some relative failures, slavery would have persisted in the South and never would have existed in New England, and so forth.

Now there are some words in this little description that resonate with me. I often refer to the NIH as a confederacy of institutes and centers. And, indeed, one of the things that we escape as a result of our Constitution was a persistent confederacy, instead built a Federal Government. And we do as an institution wage war against disease and we would like to work as effectively as possible together to wage that war.

Let me just say a few things about what the current NIH looks like before I come back to the issue of perhaps what it ought to look like. I know there are some of you in the audience who have only a vague idea of what the NIH is. You have heard from a couple of institute directors today. But, indeed, we have a lot of institute directors.

Here shown in a somewhat deceptive way, and I will explain that in just a moment, we have bars representing roughly twenty-five institutes and centers, each of which is separately authorized by Congress. Virtually all of these receive an appropriation directly from Congress. Most of them, nearly all of them have the authority to issue grants. Most, but not all, have intramural research programs. But they differ dramatically with respect to their budgets, their histories, their capabilities, some differing by as much as one hundred-fold with respect to their budgetary authority.

At the top, there is something called the Office of the Director, small budget, no real authority in many ways, no grants to give out, no intramural program. We will say more about that later on.

Now let me give you one example of an institute that would be considered a very successful nation state. So this is a diagram that illustrates one of the more successful institutes, the National Cancer Institute. This actually indeed comes before your time, Rick. You are probably familiar with this diagram. It was prepared to titillate and perhaps annoy Vince DeVita when he was the director of the National Cancer Institute some years ago. The point here is not to say that it is bad that the National Cancer Institute is a strong nation state, the problem is how about the rest of the guys.

So here is the Cancer Institute with its very dramatic representation. Over here is something called "Townhouse Row," National Institutes of everything else. Here is a little outpost called the Environmental Health Sciences Institute. Here is an outhouse called Building One, it is the Office of the Director.

[Laughter.]

DR. VARMUS: And here are some other outposts of the National Cancer Institute itself, in Japan, in Beijing. Some of these speculative, some of them perhaps real. The Heart, Lung, and Blood Institute is given some status here as one of the larger institutes.

Well, how did we get to the situation where we have many institutes that have become very large and successful, others perhaps successful in their own way but much, much smaller with very different authorities?

Here is a little picture of NIH evolution, which is a useful thing to look back on if we're going to make any speculations about the future. There was a time back in the 1930s when there was one NIH, although I think it is fair to say that institute with its various powers has dissipated as a single unit. There are many ways in which the NIH has become diversified to become the confederacy that I've mentioned. The Cancer Institute being the first independently developed institute. So in 1940 we had doubled the number, but it was only two units, perfectly manageable. By 1950 there were seven, and by 1960, which is the time the Short Course at Bar Harbor was begun, there were roughly nine. Maybe we can go to that next overhead and come back to this.

So this is how the NIH looked compared to the organizational chart I showed you a moment ago. Actually one of these things disappeared from the NIH, this became part of the FDA. But otherwise you can see that this is a pretty manageable situation.

Back to the original. Now over the course of years, some institutes began to branch off. For example, the Aging Institute became an offshoot of the Child Health Institute, the Neurology Institute, which originally had blindness in its title, became the Eye Institute and then further branched off to generate the so-called Deafness and Communications Disorders Institute. And there have been a number of other similar fissions.

Well now we are up to twenty-five institutes and centers, as I've mentioned. That's roughly nearly a tripling since 1960. I think it is fair to say there is a reasonable likelihood that this number will continue to grow and that forty years from now we'll be dealing with an institution called the NIH which is a confederacy of not twenty-five units, but more like fifty or seventy-five in the progression, depending on whether it is arithmetic or geometric, and possibly even more.

Well how do these new institutes and centers get developed? Here's one example of something that could happen in the fairly near future. The National Institute of Diabetes, Digestive, and Kidney Diseases has at least four components that could become independent institutes; indeed, there are advocacy groups that push for the formation of these independent unitsæa National Institute of Diabetes, a National Institute of Digestive Diseases, a National Institute of Urology, and a National Institute of Kidney Disease. Whether these will become a reality or not remains to be seen, but there is the potential for this one institute to become four.

There is a method for generating a new institute that derives from the establishment of an office, conversion of an office into a center with varying degrees of authority, and then conversion of the center into an institute. For example, in 1992 there was established in the Office of the Director an Office of Complimentary Medicine Research. That became converted to a national center with grant-making authority in 1998 with a conversion of a $12 million budget to a $50 million budget. I think in due course it is very likely this too will become a full-fledged institute.

We have heard discussions about the Genome Institute. That was initially established as an office and then quickly converted to a center in 1989, and in 1997 was converted to a full-

fledged institute. The Nursing Institute was begun as a center. Are other examples of this kind of transition are waiting in the wings? Well, yes, indeed, there are.

Here are a number of offices and centers that don't have independent grant-making authority at present, including the Office of AIDS Research, the Center for Medical Rehabilitation Research, Office of Research on Women's Health, a Sleep Disorders center, and Office of Research on Minority Health, and Office of Rare Diseases, Dietary Supplements, and Behavioral and Social Sciences Research. All of these, of course, in the minds of those who are advocating for the strengths of these offices be candidates for conversion to independent centerhood or institute status.

Indeed, there are proposals on the floor of the Congress for making some of these conversions. One is a total independent creation that would convert what is currently a fairly informal bioengineering consortium into a National Institute of Biomedical Imaging and Engineering, a proposal to convert the Office of Minority Health Research into a National Center for Research on Domestic Health Disparities, and a new proposal to establish an Office of Auto-immune Diseases which in the course of time would be likely to be converted into a grant-making independent organization.

So given all of this, let me just say a couple of things about why I think this is already a bit of a problem and is going to become a bigger problem in the not so distant future.

One problem comes about at the time of budget allocation, because everyone who is a fan of one of these institutes is very carefully watching its budgetary portion. That's not unexpected and, indeed, that works quite well for raising the NIH budget, and that's one of the issues we'll have to deal with in just a moment. But one of the things you'll notice is that these percentage increases tend to be pretty uniform. The Genome Institute is an exception with a more robust

increase because everyone recognizes that this is in a phase of escalation, but also the base number is relatively small and one can afford to provide something of an increase in percentage points that is better than other institutes.

Although the institute directors give a great deal of credence to the significance of these numbers, indeed the differences are really rather small. If somebody from outside the system were to come in and say where is the best management, where are the best opportunities, where are the greatest needs, it seems to me unlikely that we would be providing increments above the inflationary base that are so similar in character. Indeed, it is difficult to provide differences that reflect the real scientific needs and opportunities that reflect the kinds of changes that are occurring in our science.

Why do we have such tremendous differences in the size of the budget? Well one of the reasons is, frankly, the age of the institute. Here is a plot of institute age versus budget. As you can see, oldest at the top, the budget is shown by the length of the bar. There are some exceptions; for example, the Mental Health Institute. But there is an explanation for that. The Mental Health Institute actually was outside the NIH for many years between its founding in 1946 and its return to the NIH in 1992, and there is no doubt that it suffered budgetarily as a result of its removal from the NIH which tends to be a resource-generating agency. Another exception is the Dental Institute, and I'm not quite sure why that is. But as you can see, for the most part there is a pretty good correlation between the age of the institute and the size of its budget.

This seems like a somewhat irrational way to do budgeting and one might ask whether in fact we shouldn't relook at these numbers and see whether that evolved as a consequence of the birth date really represent the way in which funding should be undertaken.

There are complexities to the management of NIH as a result of all this that I and the institute directors have been talking about directly in part as a result of a recent budget retreat in which we began to recognize that there is a problem when we try to do things that affect many institutes or achieve technical advances that are desired by many institutes because for many institutes it is very difficult to play in endeavors that have a trans-institute character, and the sheer complexity of the institution, with its many separately appropriated budgets, makes it difficult to coordinate. You can't have a committee for every damn thing you try to do. So we all sense the cumbersomeness of an organization as diverse as ours has come to be in an age in which the science itself has become so complex that we need to bring people together despite whatever walls may have been created or separation that may have been created by the way in which the NIH has evolved.

So given all that, what can we do in the future to try to rectify this? I think at some point in the next forty years we are going to have to grapple with the fact that the NIH organization is going to have to change, whether it is now with twenty-five institutes or thirty years from now when we have sixty I think is a moot point. Although I would say to the journalists in the audience I am having fun here. I am not recommending anything specific. I am disturbed to see the number of journalists who are in the audience. You can take notes, that's fine, but I'm not prescribing anything. I am just being provocative about what might happen and outlining the need to do something sometime. And it may be on my ninetieth birthday when I am long gone from the NIH, so I am not advocating anything happening today.

But I think we have to think now, perhaps because we are at a moment of relative popularity, we need to think about what the appropriate future might be for the NIH. And, indeed, this is going to be a difficult thing to take on intellectually because it is going to have

political ramifications. Indeed, the complex organization you see is the result of a political process that in general has worked well for the NIH. Indeed, it is responsible for many aspects of our financial success and we need to think carefully before we say exactly how we're going to proceed in trying to make a more rationally devised organization.

At some point I predict we will need to establish some kind of special commission that has the blessing of the White House and the Congress and the scientific community and then try to proceed with devising something more rational.

Just for fun, this is for fun, press, I put together one kind of proposal that might emerge from such a commission's efforts. That would be a much simpler NIH that is organized into a series of large units that resemble in size the National Cancer Institute and combine the efforts that are made by a variety of institutes. I think you will find it is not all that difficult to see who might go where, but it's actually not that simple. My own prediction is we wouldn't try to move institutes and just do a fusion, but instead reorganize the science the institutes do in a rational way.

So the first new entity would be the National Brain Institute. One model for how this might happen is currently visible in the NIH planning process because virtually all the institutes that do neuroscience research at the NIH, and you know who they areæthe National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, the Institute of Alcoholism and Alcohol Abuse, and so forthæhave pooled together to generate an intramural center which is going to be proposed for incorporation into a new building on the NIH campus to replace two existing buildings that have passed their prime, and that Center for Brain Research would be in a sense one aspect of what could become a National Brain Institute.

The National Institute of General Medical Sciences is not what you think it is. It is not the current NIDMS. Instead, what I am envisioning is an institute that pays attention to the disorders that basically are treated by internists; that is, the diseases that are now under study by NIDDK, talked about earlier, under study by the National Institute of Arthritis and Muscular, Skeletal, and Skin Diseases, and a variety of other institutes.

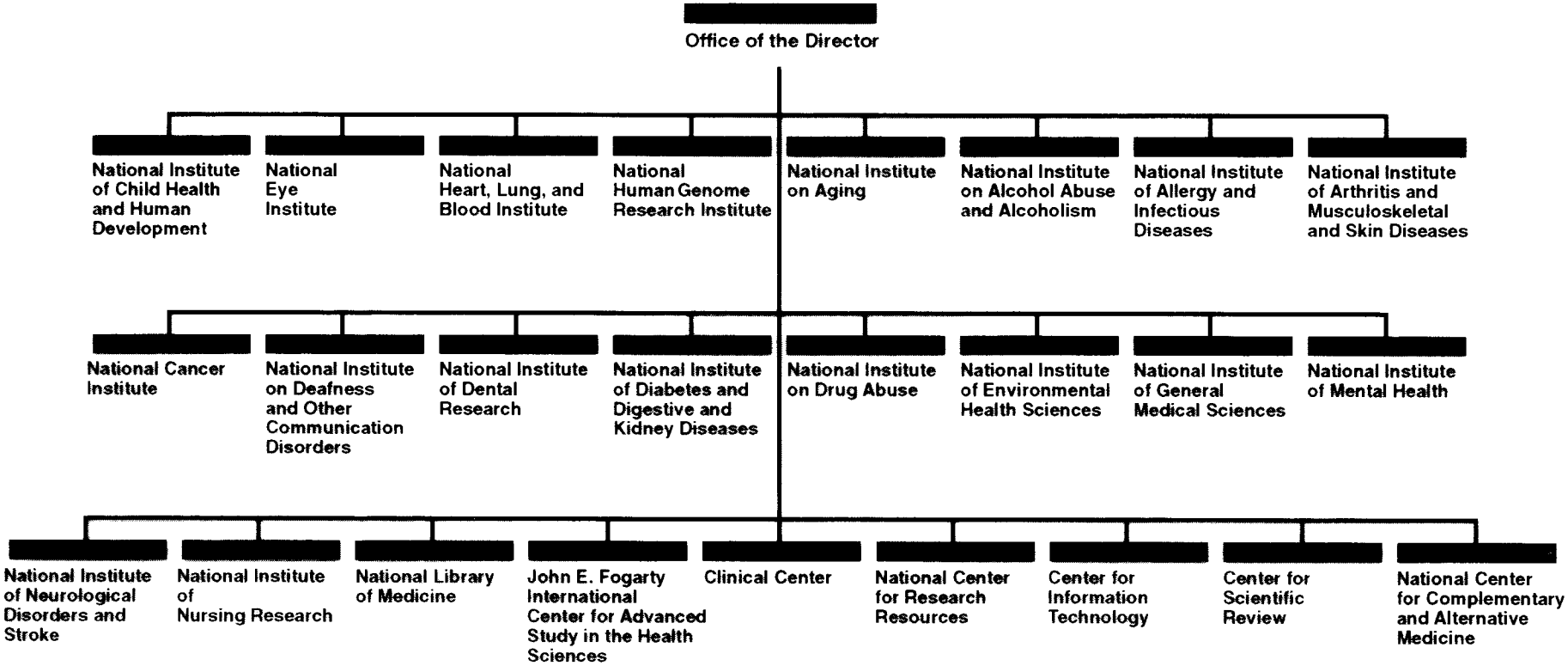
We might have an institute that is devoted to human development which would include activities in childhood, in aging, perhaps genomics and genetics. And then an institute that deals with the external factors that affect human healthæmicrobial and environmental impacts on human organisms.

And then there would be something called NIH Central, which would be a place that provided some direction in NIH policy, would oversee the infrastructure of the NIH, would allow the funding of activities that produce technologies that enable research across the institutes with a flexible budget that could come and go depending on technological needs, would coordinate international research, did some of the training and peer review that is not in the purview of the five or six other institutes, it might have some coordinating offices for special activities, and it would also house the Library of Medicine, the Clinical Center, and Information Technology. So this would provide to the NIH director a much greater portfolio of things to do, and would I think in a better way allow for special initiatives that can go up and come down in funding without addicting us to a commitment base of funding that can't decline with the project is done.

So I throw this out as one way of trying to bring greater sense to the organization of the NIH. It is not something that is going to happen in my lifetime as director. But I think on the occasion of this reflection on the forty years of the Course, the seventy years of Jacks, the hundred years of genetics, it is appropriate to take a look at the agency that has funded a lot of the

research done here and elsewhere and think, is this the best organization for dealing with the next forty years and, indeed, the next century? Thanks very much.

NIH in 1999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National Eye Institute
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National Institute on Aging
National Institute on Alcohol Abuse and Alcoholism
National Institute of Allergy and Infectious Diseases
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Cancer Institute
National Institute on Deafness and Other Communication Disorders
National Institute of Dental Research
National Institute of Diabetes and Digestive and Kidney Diseases
National Institute on Drug Abuse
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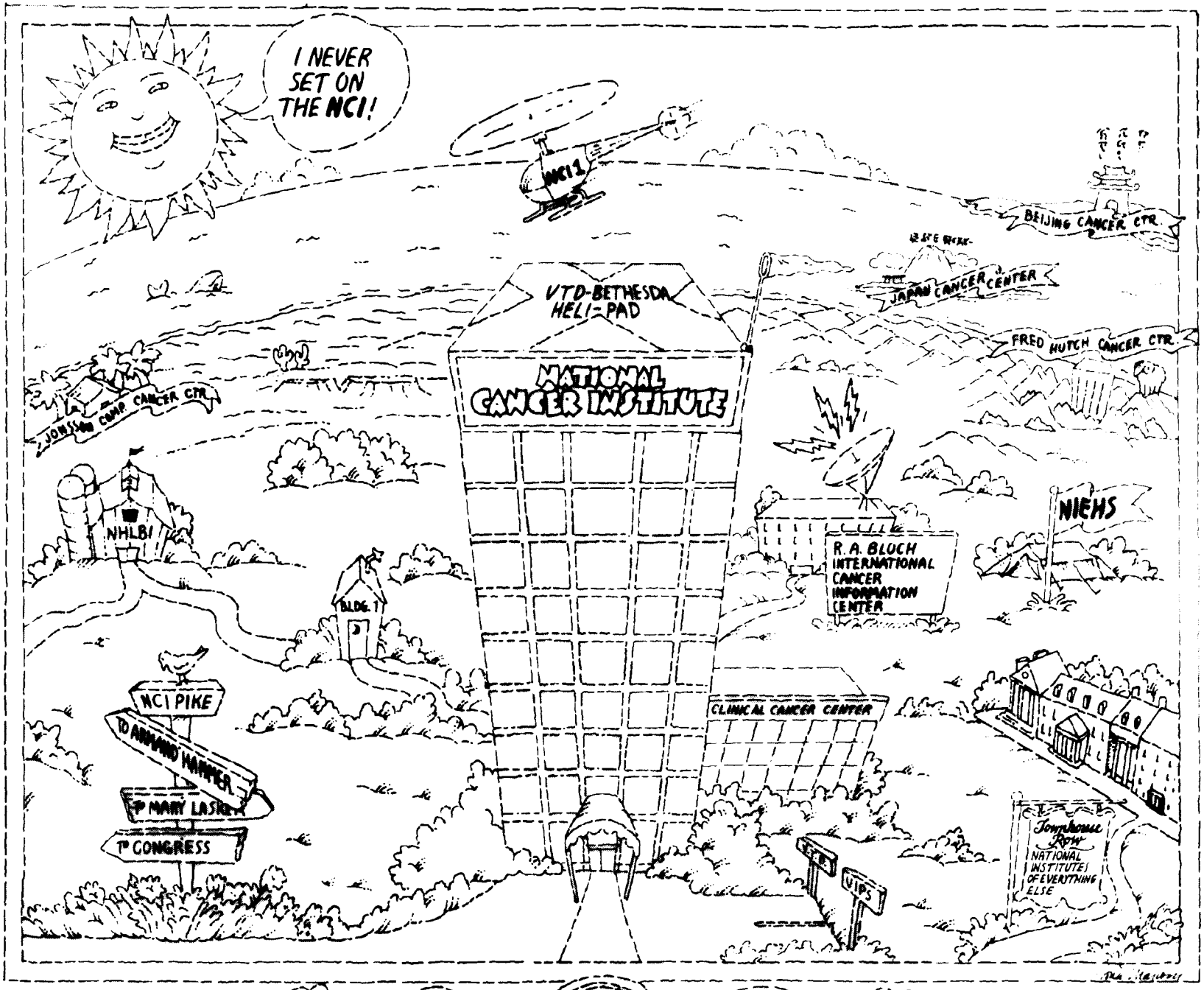

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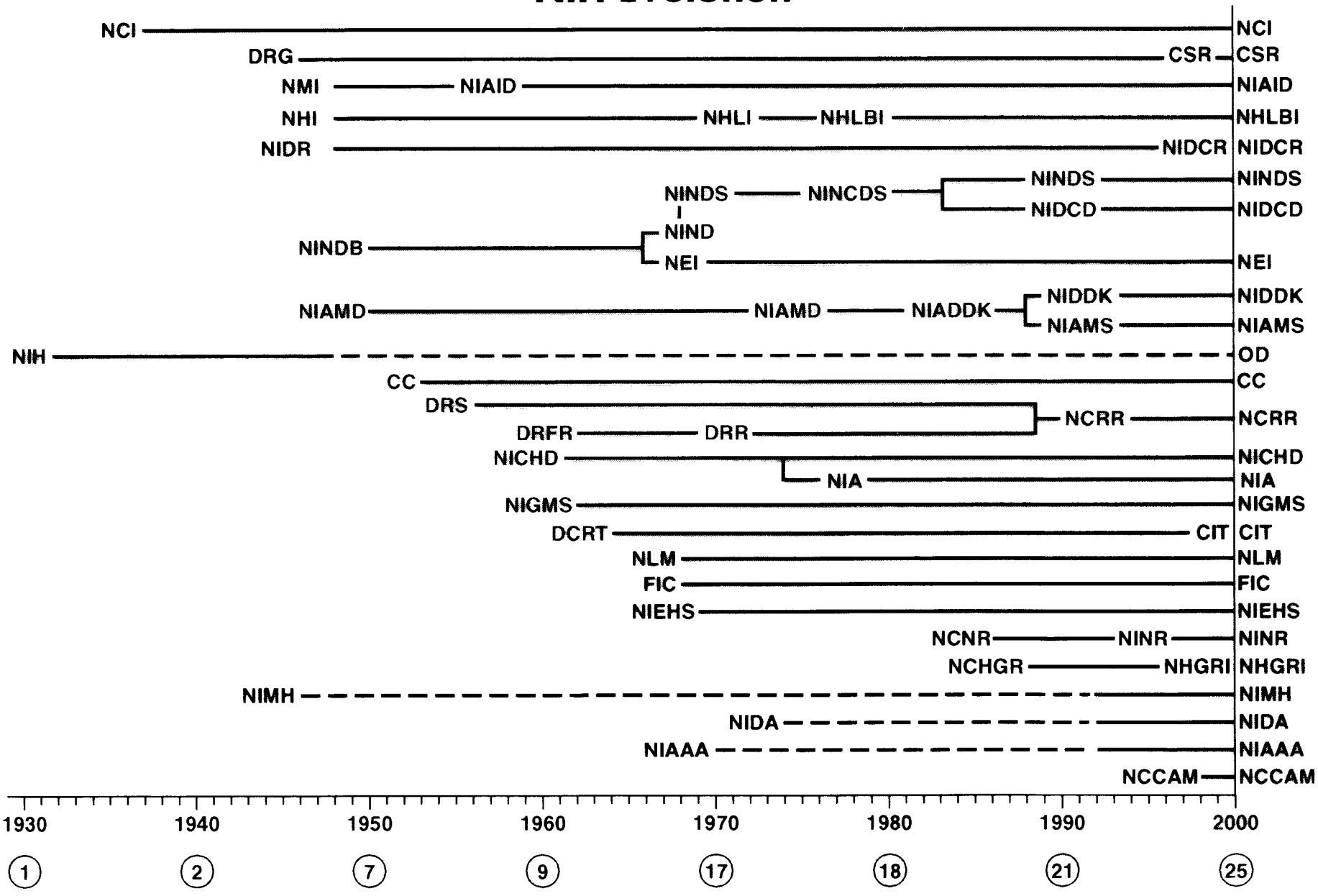
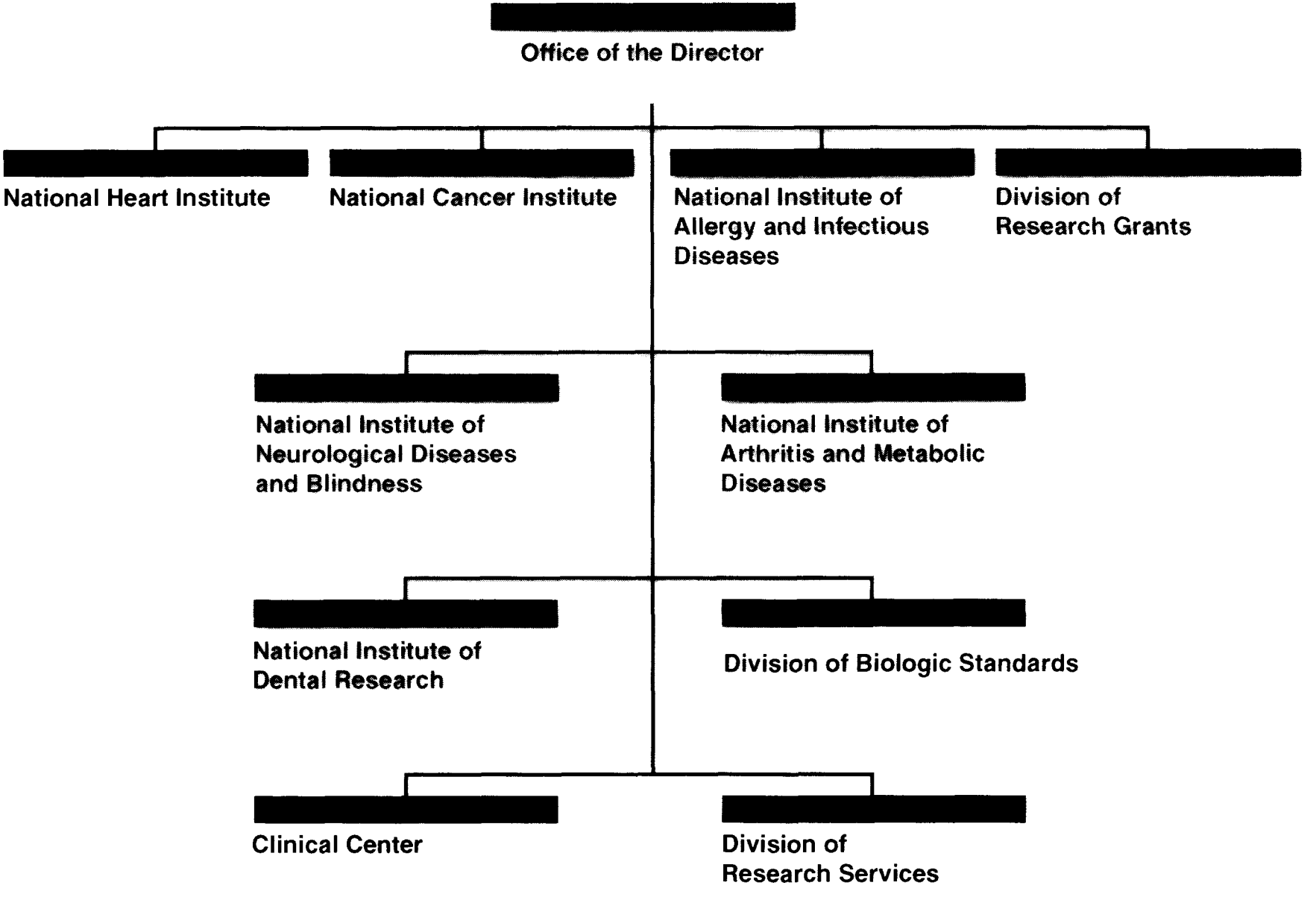
NIH Evolution



NIH in 1960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Clinical Center
Division of Research Services

A Modest Proposal for a Simpler NIH

- National Cancer Institute
- National Brain Institute
- National Institute of General Medical Sciences
- National Institute of Human Development
- National Institute of Microbial and Environmental Medicine
- NIH Central